

(19)



Europäisches Patentamt

European Patent Office

Office européen des brevets



(11)

EP 1 258 468 A1

(12)

EUROPEAN PATENT APPLICATION

(43) Date of publication:

20.11.2002 Bulletin 2002/47

(51) Int Cl.7: **C07C 29/147**, C07C 31/20,
C07C 33/26

(21) Application number: **02253047.1**

(22) Date of filing: **30.04.2002**

(84) Designated Contracting States:

**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE TR**

Designated Extension States:

AL LT LV MK RO SI

(30) Priority: **11.05.2001 US 290434 P**

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(54) **Methods for reduction of substituted malonates to diols**

(57) A method for reducing a malonate having the formula $R^1R^2C(CO_2R^3)(CO_2R^4)$ to a diol having the formula $R^1R^2C(CH_2OH)_2$ comprising treating said malonate with sodium aluminum hydride.

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DescriptionBackground

[0001] This invention relates generally to a method for reducing substituted malonates to diols using sodium aluminum hydride.

[0002] Substituted malonates have been reduced to the corresponding diols with lithium aluminum hydride or with lithium borohydride, as described in U.S. Patent No. 4,982,016. However, reduction of substituted malonates with sodium aluminum hydride has not been reported.

[0003] Sodium aluminum hydride typically is available commercially as a slurry in toluene at a lower cost than lithium aluminum hydride or lithium borohydride. A method for reducing substituted malonates to diols, without using lithium aluminum hydride or lithium borohydride would be more economical and would be commercially valuable.

Statement of Invention

[0004] The present invention is directed to a method for reducing a malonate of formula $R^1R^2C(CO_2R^3)(CO_2R^4)$ to a diol of formula $R^1R^2C(CH_2OH)_2$ comprising treating said malonate with sodium aluminum hydride; wherein R^1 is aryl, alkyl, aralkyl, alkenyl, or alkynyl; R^2 is hydrogen, aryl, alkyl, alkenyl, or alkynyl; and R^3 and R^4 are independently alkyl or aralkyl.

Detailed Description

[0005] Unless otherwise specified, all percentages herein are stated as weight percentages, temperatures are in °C, and volumes in mL.

[0006] An "alkyl" group is a saturated hydrocarbyl group having from one to twenty carbon atoms in a linear, branched or cyclic arrangement. Preferably, alkyl groups have from one to twelve carbon atoms, and most preferably, from one to six carbon atoms. An "alkenyl" group is an "alkyl" group in which at least one carbon-carbon single bond has been replaced with a double bond. An "alkynyl" group is an "alkyl" group in which at least one carbon-carbon single bond has been replaced with a triple bond. Preferably, alkyl, alkenyl and alkynyl groups are acyclic and unsubstituted. Alkyl, alkenyl and alkynyl groups optionally are substituted with one or more hydroxy, halo, alkyl, alkenyl, alkoxy, amino or alkylamino groups, with substitution by one or more halo groups being possible on alkyl or alkoxy groups. An "aryl" group is a substituent derived from an aromatic compound, including heterocyclic aromatic compounds having at least one nitrogen, oxygen or sulfur atom in the ring. An aryl group has a total of from five to twenty ring atoms, and has one or more rings which are separate or fused. Preferably, aryl groups have from five to ten ring atoms. Substitution on aryl groups of one or more hydroxy, halo, alkoxy, alkyl, alkenyl or alkynyl groups is permitted, with substitution by one or more halo groups being possible on alkyl, alkenyl or alkoxy groups. An "aralkyl" group is an "alkyl" group substituted by an "aryl" group.

[0007] In one embodiment of the invention, R^1 is aryl and R^2 is hydrogen. Preferably, R^1 is phenyl and R^3 and R^4 are alkyl, i.e., the substituted malonate is a dialkyl phenylmalonate. R^3 and R^4 represent the same alkyl group or different alkyl groups. The 2-phenyl-1,3-propanediol product obtained in this embodiment is useful as an intermediate for the corresponding diol dicarbamate compound, an important intermediate in the dye industry and in pharmaceutical applications. In another embodiment of the invention, R^1 and R^2 are alkyl, wherein R^1 and R^2 are the same or different alkyl groups. Preferably, R^1 and R^2 are n-butyl and R^3 and R^4 are alkyl, wherein R^3 and R^4 are the same or different alkyl groups.

[0008] Typically, the method of this invention is performed in an ethereal solvent in which sodium aluminum hydride is soluble, for example, tetrahydrofuran ("THF") or glymes. Suitable glymes include, for example, monoglyme (dimethoxyethane), diglyme (2-methoxyethyl ether), triglyme (triethylene glycol dimethyl ether), and tetraglyme (tetraethylene glycol dimethyl ether). The preferred solvent is THF. The preferred temperature range for the reduction is from -90°C to 150°C, more preferably from 25°C to 90°C, and most preferably from 40°C to 75°C. The reduction reaction is continued until the substituted malonate starting material has been substantially consumed. The preferred reaction time is from 0.1 hours to 48 hours, more preferably from 6 hours to 40 hours, and most preferably from 8 hours to 30 hours. Preferably, the amount of SAH, relative to the amount of malonate, is from 1 to 10 equivalents, more preferably from 1 to 5 equivalents, and most preferably from 1 to 2 equivalents. In one embodiment of the invention, sodium aluminum hydride ("SAH") is introduced in the form of a slurry comprising SAH and toluene. Preferably, the slurry has from 1% to 75% SAH and from 25% to 99% toluene, more preferably from 10% to 60% SAH and from 40% to 90% toluene, and most preferably from 30% to 50% SAH and from 50% to 70% toluene.

Example

Conversion of Diethyl 2,2-Dibutylmalonate to 2,2-Dibutyl-1,3-propanediol

[0009] An oven-dried 1000 mL three-neck flask containing a magnetic stir bar was purged with nitrogen gas and charged with 30 g of sodium aluminum hydride and 250 mL of anhydrous tetrahydrofuran ("THF"). To this solution was added drop-wise, so that the reaction temperature remained below 60°C, a solution of 100 g diethyl 2,2-dibutylmalonate in 150 mL of THF. After completion of the addition (3-4 hours), the reaction mixture was heated to 50°C and maintained at that temperature for 24 hours, after which the solution was cooled to room temperature. Methanol was added drop-wise until all of the excess aluminum hydride had been consumed, followed by 350 mL of saturated aqueous sodium chloride solution. The resulting mixture was separated and extracted three times with 250 mL portions of THF, and the combined THF layers were dried over anhydrous magnesium sulfate for five hours. The solvent was removed in vacuo, resulting in a slightly yellow syrupy sample. To this sample was added 100 g hexane, followed by removal of the solvent in vacuo. The residue was placed in a freezer at -22°C, where after a few hours, the sample solidified. Hexane (5 g) was added to the solid, which was then collected on a glass frit filter and washed with two ten-gram portions of hexane. The crystals were dried in air. Subsequent freezing of the filtrate produced two more crops of crystals, and addition of small amounts of hexane to the filtrate followed by freezing produced another two crops.

Weight of product:	
Fraction 1	36.21 g
Fraction 2	16.48 g
Fraction 3	1.51 g
Fraction 4	3.80 g
Fraction 5	0.8 g
Total (% yield)	58.8 g (85.2%)

[0010] The results from the Example, and from additional reduction experiments are summarized in the following Table. Each experiment started with 100 g of diethyl 2,2-dibutylmalonate and used THF as a solvent, or a mixture of THF and toluene in cases where the metal hydride is used in the form of a toluene slurry. The metal hydrides used were sodium aluminum hydride ("SAH"), lithium aluminum hydride ("LAH"), sodium bis-(2-methoxyethoxy)aluminum hydride ("SDMA") or lithium borohydride ("LBH") with trimethoxyborate ("TMB"). Reaction times are given in hours, and reaction temperatures in °C, as "reflux" (reflux temperatures not measured), or as "r.t." (room temperature).

Table

Metal Hydride	Amount (equiv.)	Reaction Temp.	Reaction Time	Crude Weight	% Yield
SAH	1	50°C	8	36.1 g	58
SAH	1.5	50°C	12	51.75 g	75
SAH	2	50°C	24	58.8 g	85.2
45% SAH/toluene	1.5	50°C	24	61.42 g	89.00
LAH	1	50°C	24	22.65 g	32.82
45% LAH/toluene	1.5	50°C	24	28.49 g	41.28
LAH	2	50°C	24	50.66 g	73.40
SDMA	2	r.t.	22	--	25 ¹
SDMA/toluene	2	reflux	6	--	39 ¹
SDMA	2	reflux	9	--	32 ¹
LBH/0.2 TMB	2	60°C	18	--	0.00

1. Yield determined by gas chromatography; product not isolated.

Claims

1. A method for reducing a malonate of formula $R^1R^2C(CO_2R^3)(CO_2R^4)$ to a diol of formula $R^1R^2C(CH_2OH)_2$ comprising treating said malonate with sodium aluminum hydride; wherein R^1 is aryl, alkyl, aralkyl, alkenyl, or alkynyl; R^2 is hydrogen, aryl, alkyl, alkenyl, or alkynyl; and R^3 and R^4 are independently alkyl or aralkyl.
2. The method of claim 1 in which R^1 is aryl, alkyl, aralkyl, alkenyl or alkynyl; and R^2 is hydrogen or alkyl.
3. The method of claim 2 in which R^1 is aryl and R^2 is hydrogen.
4. The method of claim 3 in which R^1 is phenyl and R^3 and R^4 are alkyl.
5. The method of claim 4 in which R^3 and R^4 are ethyl.
6. A method for reducing a malonate of formula $R^1R^2C(CO_2R^3)(CO_2R^4)$ to a diol of formula $R^1R^2C(CH_2OH)_2$ comprising treating said malonate with sodium aluminum hydride; wherein R^1 is alkyl; R^2 is alkyl; and R^3 and R^4 are independently alkyl or aralkyl.
7. The method of claim 6 in which R^1 and R^2 are n-butyl and R^3 and R^4 are alkyl.
8. The method of claim 7 in which R^3 and R^4 are ethyl.
9. A method for reducing a malonate of formula $R^1R^2C(CO_2R^3)(CO_2R^4)$ to a diol of formula $R^1R^2C(CH_2OH)_2$ comprising treating said malonate with sodium aluminum hydride; wherein R^1 is aryl, alkyl, aralkyl, alkenyl, or alkynyl; R^2 is hydrogen, aryl, alkyl, alkenyl, or alkynyl; and R^3 and R^4 are independently alkyl or aralkyl; wherein the sodium aluminum hydride is introduced as a slurry comprising sodium aluminum hydride and toluene.
10. The method of claim 9 in which R^1 is alkyl and R^2 is alkyl.



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EUROPEAN SEARCH REPORT

Application Number
EP 02 25 3047

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The present search report has been drawn up for all claims			
Place of search MUNICH		Date of completion of the search 22 August 2002	Examiner Herzog, A
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

EPO FORM 1503 03.02 (P04C01)



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Application Number
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**ANNEX TO THE EUROPEAN SEARCH REPORT
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22-08-2002

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